THE STRUCTURE OF MONOCROTALIC ACID

BY
JOSEPH MARION WILKINSON, JR.
B.Ed., Southern Illinois State Normal University, 1938
M.S., University of Illinois, 1940

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1943

URBANA, ILLINOIS
1943

THE STRUCTURE OF MONOCROTALIC ACID

BY
JOSEPH MARION WILKINSON, JR.
B.Ed., Southern Illinois State Normal University, 1938
M.S., University of Illinois, 1940

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1943

URBANA, ILLINOIS
1943

ACKNOWLEDGMENT

The writer wishes to express his sincere appreciation to Professor Roger Adams for his many helpful suggestions and his encouraging interest during the course of these investigations.

THE STRUCTURE OF MONOCROTALIC ACID

Introduction and Historical

Monocrotaline, an alkaloid from the *Crotalaria spectabilis*, was shown to have the empirical formula $C_{16}H_{23}O_6N$.[1] Alkaline hydrolysis gives the alkanolamine, retronecine, and monocrotic acid, $C_7H_{12}O_3$, which has been shown to be α,β-dimethyllevulinic acid.[2] Hydrogenolysis of the alkaloid yields the base, retronecanol, and monocrotalic acid, $C_8H_{12}O_5$, which is believed to be esterified with retronecine in the alkaloid.

The work of Adams, Rogers, and Long[3] indicates that monocrotalic acid is related closely to α,β-dimethyllevulinic acid and possesses the following properties: Monocrotalic acid loses carbon dioxide in the presence of alkali to give monocrotic acid; back titration of the acid from excess alkali indicates a lactone linkage; thermal decomposition gives α,β-dimethylangelicalactone; the monomethyl ester possesses one active hydrogen which presumably is involved in a tertiary hydroxyl group; thermal dehyration of the methyl ester yields an unsaturated ester which can be reduced to a saturated ester and hydrolyzed to a stable lactonic acid; hydrolysis of the unsaturated ester yields a lactone identical with that obtained by the thermal decomposition of monocrotalic acid.

On the basis of these observations, it appeared that monocrotalic acid was α-carboxy-α,β-dimethyl-γ-hydroxy-γ-valerolactone (I), β-carboxy-α,β-dimethyl-γ-hydroxy-γ-valerolactone (II), or δ-carboxy-α,β-dimethyl-γ-hydroxy-γ-valerolactone (III). Structures I and II seemed improbable since synthesis of ethyl α-carbethoxy-α,β-dimethyllevulinate and ethyl β-carbethoxy-α,β-dimethyllevulinate followed by either alkaline or acidic hydrolysis did not yield monocrotalic acid but α,β-dimethyllevulinic acid.[4] Structure III, therefore, seemed most likely, and it is the attempts to investigate the validity of this structure by degradative and synthetic reactions that form the basis of this work.

Theoretical and Discussion of Results

Monocrotalic acid was converted to a crystalline acid chloride by thionyl chloride. Treatment of the acid chloride

with methanol yielded methyl monocrotalate which was identical with the product obtained by the action of diazomethane on monocrotalic acid.

Prolonged heating of monocrotalic acid with thionyl chloride gave anhydromonocrotalic acid which apparently was formed by the removal of the elements of water from monocrotaloyl chloride and hydrolysis of the resulting unsaturated acid chloride. Treatment of anhydromonocrotalic acid with diazomethane followed by reduction and hydrolysis gave dihydroanhydromonocrotalic acid.[3] Anhydromonocrotalic acid cannot be propared by the hydrolysis of methyl anhydromonocrotalate which is obtained by the thermal decomposition of methyl monocrotalate.

The acid chloride of monocrotalic acid gave a crystalline diazoketone with diazomethane. The diazoketone was converted to the corresponding chloroketone with hydrogen chloride. However, all attempts to rearrange the diazoketone into the next higher homologous acid or its derivatives in an effort to stabilize the molecule were unsuccessful.

Treatment of methyl monocrotalate, methyl anhydromonocrotalate, and methyl dihydromonocrotalate[3] with ammonia in an attempt to form the substituted pyrrolidones gave the respective amides. Had the pyrrolidones been formed, it was hoped that they could be reduced and dehydrogenated to the substituted pyrrole which might be available synthetically.

Oxidation of monocrotalic acid with nitric acid gave α,β-dimethylmaleic anhydride as the only crystalline degradation product. The presence of acetic acid in the oxidation mixture was suspected as the result of a positive lanthanum nitrate test;[5] attempts to obtain a quantitative estimation of the acetic acid were unsuccessful. However, a compound of structure III would be expected to yield the products identified. Oxidation of monocrotalic acid with acidic potassium permanganate gave acetic acid as the only degradation product that could be isolated. The acetic acid was identified through its crystalline *p*-bromophenacyl ester.

The successful conversion by Quadrat-I-Khuda and Ghosh[6] of δcarbethoxy-α,β,γ-trimethyl-γ-valerolactone into

ethyl α,α,γ-trimethyl-γ-chloroadipate suggested that such a reaction might be applicable to methyl dihydroanhydromonocrotalate. Thus, with phosphorus pentachloride, the lactone of methyl dihydroanhydromonocrotalate would be cleaved, and subsequent esterification of the acid chloride would yield methyl α,β-dimethyl-γ-chlorodipate. Reductive removal of the chlorine would then yield methyl α,β-dimethyladipate which should be available synthetically. Treatment of methyl dihydroanhydromonocrotalate with phosphorus pentachloride gave a crystalline compound which did not contain chlorine. The analysis of the product indicated $C_{10}H_{14}O_7$ as the molecular formula; however, such a formula does not agree with any obvious structure that one might write for the product of such a reaction.

The addition of potassium cyanide to the lactone of methyl dihydroanhydromonocrotalate in a manner analogous to that employed by Ranganathan[7] in the synthesis of ethyl δ-carbethoxy-α,α,γ-trimethyladipate appeared to be a feasible route to the substituted adipic acid. However, treatment of the lactonic ester with potassium cyanide followed by hydrolysis gave a crystalline lactonic acid which apparently was stereoisomeric with dihydroanhydromonocrotalic acid.

A possible synthesis of dihydroanhydromonocrotalic acid, which from structure III would be δ-carboxy-α,β-dimethyl-γ-valerolactone, appeared to be the lactonization of α,β-dimethylmuconic acid followed by reduction. Ethyl β-acetylacrylate was condensed with ethyl α-bromopropionate. Analysis of the resulting product indicated it to be the expected β-hydroxy ester; however, all attempts to convert the ester into ethyl α,β-dimethylmuconate were unsuccessful. Similarly, either acidic or alkaline hydrolysis of the Reformatsky product gave intractable oils as the only products. A second possible synthesis of α,β-dimethylmuconic acid might involve the bromination and dehydrohalogenation of the corresponding dimethyladipic acid. An expeditious route to the adipic acid appeared to be the condensation of ethyl β-bromopropionate with ethyl levulinate followed by dehydration and reduction. However, the condensation gave δ-carbethoxy-γ,δ-dimethyl-

γ-valerolactone (IV). Either alkaline or acidic hydrolysis of compound IV gave the crystalline δ-carboxy-γ,δ-dimethyl-γ-valerolactone.

The condensation of α,β-dimethylmaleic anhydride with acetic anhydride followed by reduction should yield a compound with a structure analogous to that proposed for dihydroanhydromonocrotalic acid. However, attempts to effect the initial condensation were unsuccessful.

In an effort to confirm structure III, ethyl-δ-carbethoxy-δ-cyano-α,β-dimethyllevulinate V) was synthesized from ethyl α,β-dimethylsuccinyl chloride and ethyl cyanoacetate. Hydrolysis of this ester followed by decarboxylation and spontaneous lactonization was expected to yield either monocrotalic acid or its amide. Hydrolysis of compound V with boiling alkali or acid resulted in oils which failed to crystallize; however, hydrolysis with dilute alkali at room temperature yielded a crystalline product. Difficulty was encountered in the purification of the product, and although no satisfactory analysis could be obtained, nevertheless, δ-cyano-α,β-dimethyllevulinic acid (VI) appeared to be the most likely structure. Acid hydrolysis of compound VI would be expected to yield monocrotalic acid of structure III; however, no crystalline acid could be isolated from the hydrolysis.

Bibliography

1. Adams and Rogers, J. Am. Chem. Soc., **61**, 2815 (1939).
2. Adams, Rogers, and Sprules, **ibid.**, **61**, 2819 (1939).
3. Adams, Rogers, and Long, **ibid.**, **61**, 2822 (1939).
4. Adams and Long, **ibid.**, **62**, 2289 (1940).
5. Kruger and Tschirch, Mikrochem., **2**, 337 (1930).
6. Quadrat-I-Khuda and Ghosh, J. Ind. Soc., **16**, 287 (1939).
7. Ranganathan, **ibid.**, **14**, 266 (1937).

VITA

The writer was born in Marion, Illinois, on January 3, 1917. He received his elementary education in the public schools of that city. He entered the Southern Illinois State Normal University in September, 1934, and received the degree of Bachelor of Education in June, 1938. He was enrolled in the Graduate School of the University of Illinois from the fall of 1938 to the spring of 1943. In February, 1940, the degree of Master of Science was conferred. He held a teaching assistantship in the University of Illinois during the years 1938-1943.

Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41549818_0209